A complex chromosomal rearrangement in a child with developmental delay, fractious behavior, and craniofacial anomalies, compatible with Smith-Magenis Syndrome

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INTRODUCTION

Smith–Magenis syndrome (SMS) (OMIM No 182290) is a mental retardation syndrome characterised by behavioural abnormalities, including self injurious behaviour, sleep disturbance, and distinct craniofacial and skeletal anomalies. It is usually associated with deletion involving 17p11.2 and is estimated to occur in 1/25 000 births[1]. Approximately 90% of SMS cases have the 17p11.2 microdeletion[2]. Mutations leading to protein truncation in retinoic acid induced 1 gene (*RAI1*) have been identified in some individuals with phenotypic features consistent with SMS. *RAI1* lies within the 17p11.2 locus, but these patients did not have 17p11.2 deletions[1].
Complex chromosome rearrangements (CCRs) are structural chromosome anomalies involving >2 chromosomes or >2 breakpoints[3].
Evaluation of CCRs and their potential phenotypic consequences is a common challenge in the genetics clinic and knowledge about the genotype/phenotype relationships are limited[3,4,5].

METHODS

We report the case of a 14-year-old boy who was referred by SMS, presenting mental developmental delay, fractious behavior, reduced sensitivity to pain, macrocranium, speech delay, and distinctive facial features with face dismorfology, inaccurate teeth implanting and low ears implantation .
The karyotype and fluorescence *in situ* hybridization (FISH) using WCP specific probes for the chromosomes involved in CCR and the probe D17S258 (17p11.2 probe) for SMS region, was performed by standard methods.
Chromosomal Comparative Genomic Hybridization (cCGH) and, lately, microarray studies (array CytoScan HD (Affymetrix®) were performed in order to identify genomic imbalances in the CCR breakpoints.

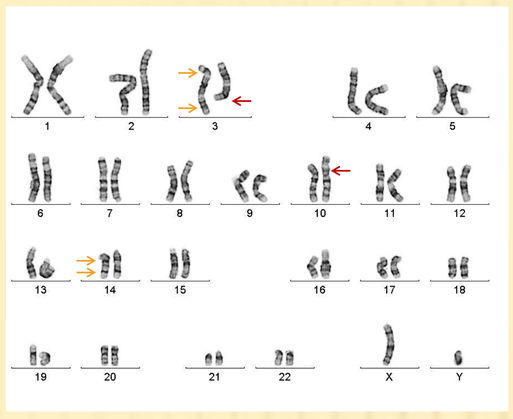


Figure 1. GTL-banded karyotype (the normal chromosomes 3, 10 and 14 are in the left and the abnormal ones are in the right.

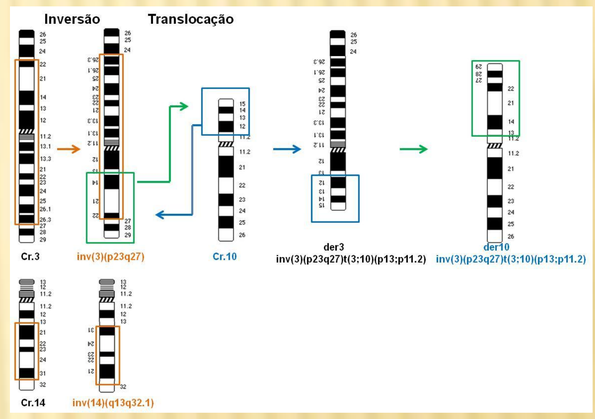


Figure 2. Idiograms of chromosomes 3, 10 and 14 involved in the CCR.

RESULTS

The cytogenetic analysis revealed a karyotype: 46,XY,inv(3)(p23q27)t(3;10)(p13;p11.2),inv(14)(q13q32)dn.ish inv(3)t(3;10)(wcp10+), der(10)t(3;10)(wcp3+),inv(14)(wcp14+) (Figures 1 and 2).
Parental karyotype were normal, although the father presented a marked cognitive delay.
FISH analyses showed no deletion in 17p11.2 region and confirmed the cytogenetic results, namely the presence of CCR involving chromosomes 3, 10 and 14 (Figures 3, 4 and 5). FISH also allows to exclude the involvement of other chromosomes in CCR .
cCGH show the no existence of gains or losses in CCR breakpoints as well in other chromosomes. Genomic microarray studies did not reveal any gains/losses of genetic material in the breakpoints regions. The whole genomic array study shows the existence of two losses (2q32.3 and 22q11.21) and one gain in 10q26.3. In the deleted region of chromosome 2 there are no localizated genes. In the deleted region of chromosome 22 there are the gene *C22orf25*(*Tango*), not associated to phenotypic alterations. In the duplicate region of chromossome 10 there are localizated various genes, with no knowlege of direct assotiation with phenotypics alterations (Figure 6).

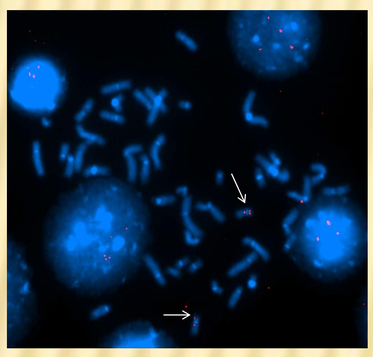


Figure 3. FISH analyses with Smith-Magenis specific probe (D17S258 - 17p11.2 probe) (red) showing signals in the two chromosomes (→)

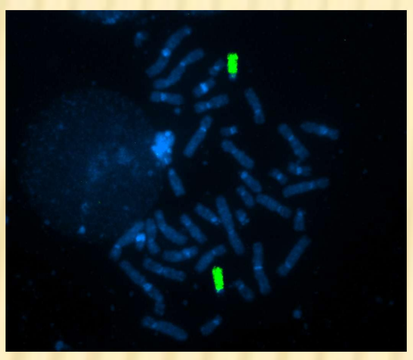


Figure 4. FISH analyses with a whole chromosome 14 painting probe (wcp14)

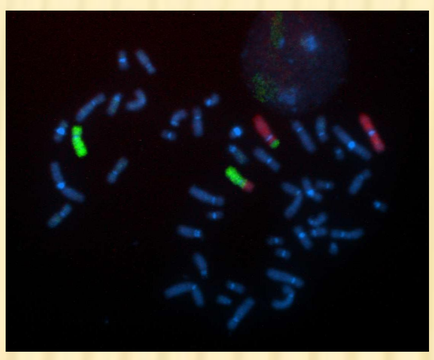


Figure 5. FISH analyses with whole cromosome painting for chromosomes 3 and 10 (wcp3 and wcp10), showing the hibridization and the translocation t(3;10).

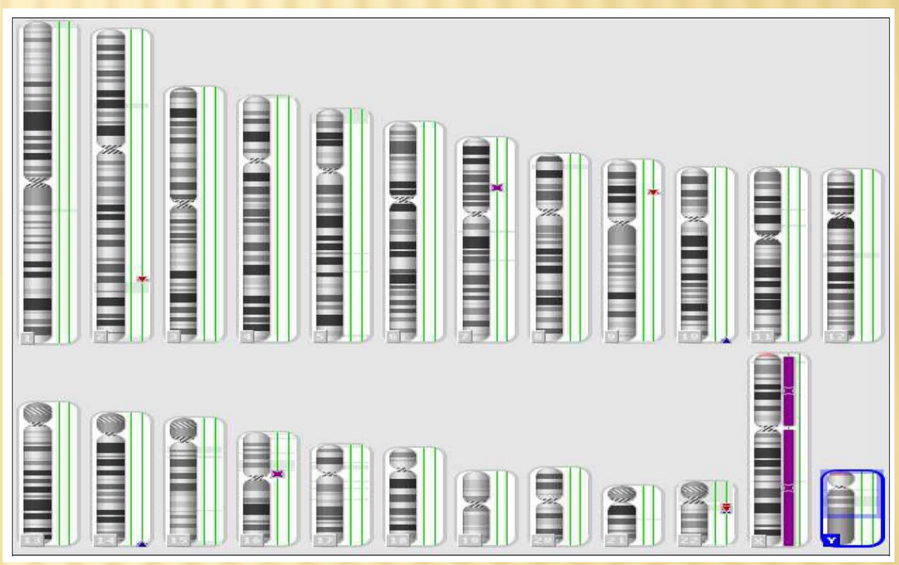


Figure 6. Whole genome microarray result s showing the existence of two losses (2q32.3 and 22q11.21), one gain (10q26.3) and no imbalances in CCR breakpoints and in 17p. Blue arrow indicates gain of genetic material, red arrow indicates loss of genetic material and purple star indicates LOH. Array Cytoscan HD Affymetrix® Cytogenetics Copy Number Assay P/N 7033038 Rev.3.; markers 2696653 (743304 SNP/1953249 non-polymorfic) probes number: 25 markers for 150 kb for gains; 35 markers for 75kb for loses and 50 markers for 3000kb for LOH. Analysis was done using the software Genotyping Console v4.0 and Chromosome analysis Suite 1.2.2 with NetAffx (ucsc hg19).

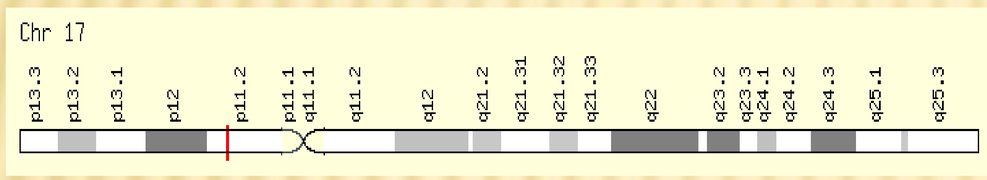
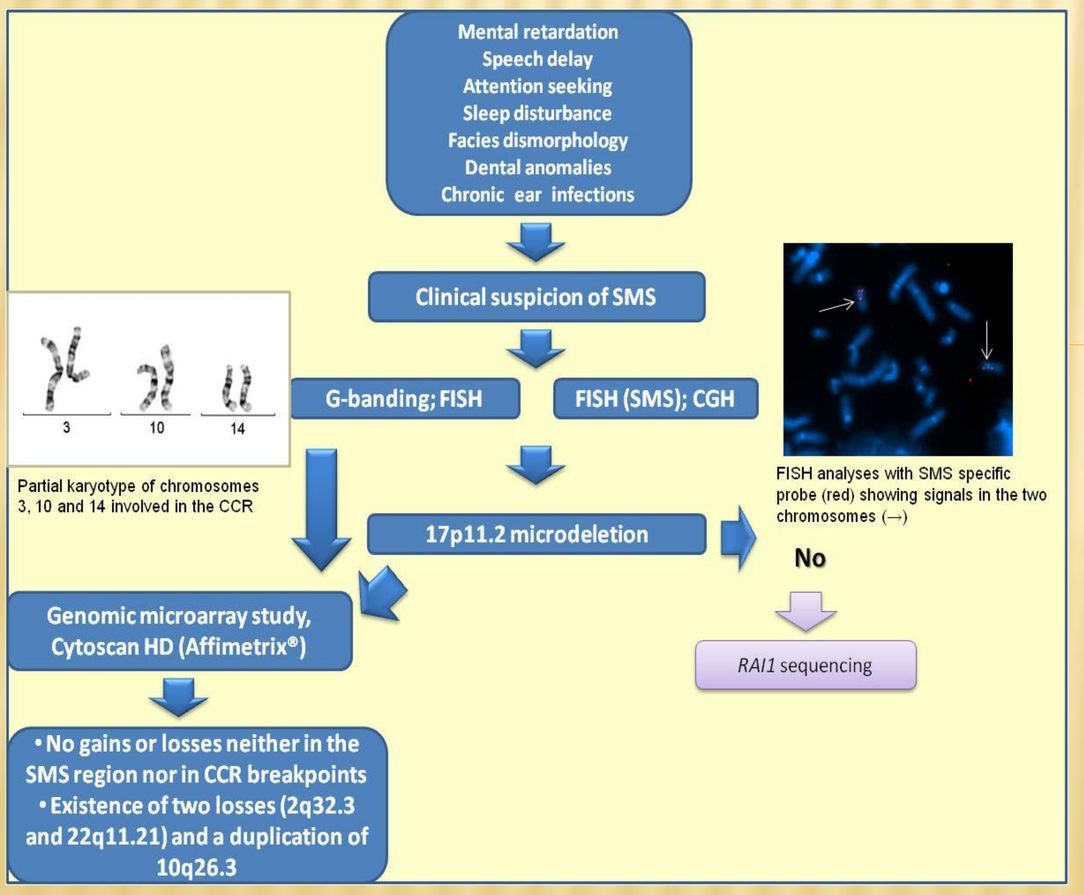


Figure 7. Chromosome 17, with region 17p11.2 and *RAI1 Gene location (−) (http://www.genecards.org/cgi-bin/carddisp.pl?gene=RAI1)*[6]

Flow chart followed for the study case at present data



DISCUSSION

The diagnosis of SMS is usually based on clinical findings and confirmed by detection of an interstitial microdeletion of 17p11.2 (ranging from 1.5 to 9 Mb, e.g. ≈3.7-Mb) that is present in, approximatelly, 90% of SMS cases. In this patient, despite the distinctive clinical features of SMS, deletions or duplications in the SMS critical region were not detected neither by FISH nor by CGH. It has been reported, however, that a small number of SMS present a mutation in the *RAI1* gene instead of a 17p11.2 deletion[2]Figure 7). In addition, the analysis of the clinical data in SMS corroborates the idea that there are very similar phenotypes among patients with a 17p11.2 deletion and those with a mutation in the *RAI1* gene[7].
In the present case, short stature, cardiac and renal anomalies were not observed, which is compatible with the phenotype reported in individuals with a *RAI1* heterozygous frameshift mutation[8,9]. However, this could not be confirmed for this patient because sequencing is still to be performed. On the other hand, chronic ear infections, speech delay, and dental anomalies, similar to those observed in our case, are more frequent in cases of del17p11.2 [2].
The patient has been absent of routine clinical reevaluation and treatment. Management of SMS is primarily a multidisciplinary approach and involves treatment for sleep disturbance, speech and occupational therapies, minor medical interventions, and management of behaviors [2].

On the other hand, a CCR was identified in the present case. It is known that in CCRs *de novo,* an apparently balanced karyotype may be associated with an abnormal phenotype, including an increased risk of intellectual delay and congenital malformations. These rearrangements can cause disease by physically disrupting genes or altering their regulatory environment[3]. The finding that 23% of the CCRs, although apparently balanced, have been ascertained among individuals with multiple congenital anomalies and/or mental retardation, and that among those with de novo occurrence, more than half have been found in individuals with phenotypic abnormalities, also suggests that imbalances may be a common finding[2]. However, the identified CCR is not a satisfactory explanation for the patient phenotype given that no imbalances were observed by the applied methods.
Additionally, following microarrays analysis, two losses (2q32.3 and 22q11.21) and one gain in 10q26.3 were identify. In the deleted region of chromosome 2 there are no localizated genes. In the deleted region of chromosome 22 is present the gene *C22orf25* (*Tango*), not associated to phenotypic alterations. In the duplicate region of chromossome 10 there are localizated various genes, with no knowlege of direct assotiation with SMS at the present data.

In summary, in the present case, the presence of the common SMS features and the occurrence of a CCR difficult the establishment of a clear genotype/phenotype relationship. Thus, further studies comprising, e.g., sequencing of the breakpoints, chromatin conformation analysis, position effect analysis as well as the refinement of the SMS critical region/RAI1 sequencing analysis might be useful to elucidate the phenotypic characteristics.

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